



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

Publication number:

**0 345 808  
A1**

12

## EUROPEAN PATENT APPLICATION

21 Application number: **89110485.3**

51 Int. Cl.<sup>4</sup>: **C07D 401/12 , C07D 401/14 ,  
A61K 31/44 , A61K 31/495 ,  
C07D 487/08**

22 Date of filing: **09.06.89**

A request for correction of pages 18, 23 and 36 of the description has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 2.2).

30 Priority: **10.06.88 US 204845  
14.04.89 US 338253**

43 Date of publication of application:  
**13.12.89 Bulletin 89/50**

84 Designated Contracting States:  
**AT BE CH DE ES FR GB GR IT LI LU NL SE**

71 Applicant: **Bristol-Myers Company  
345 Park Avenue  
New York New York 10154(US)**

72 Inventor: **Smith, David William**

**7 Silver Birch Lane  
Clinton Connecticut 06413(US)**

Inventor: **Yocca, Frank D.**

**38 Tibbals Bridge Road  
Madison Connecticut 06443(US)**

Inventor: **Yevich, Joseph Paul**

**115 Crest Road  
Southington Connecticut 06489(US)**

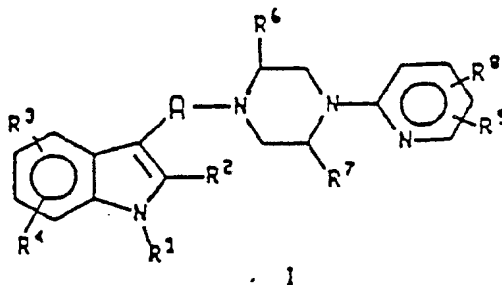
Inventor: **Mattson, Ronald John**

**65 Smithfield Avenue  
Meriden Connecticut 06450(US)**

74 Representative: **Kinzebach, Werner, Dr. et al  
Patentanwälte Reitsstötter, Kinzebach und  
Partner Sternwartstrasse 4 Postfach 86 06 49  
D-8000 München 86(DE)**

54 **1-Indolylalkyl-4-(substituted-pyridinyl)piperazines.**

57 A compound of Formula I and the pharmaceutically acceptable acid addition salts thereof,



wherein

R<sup>1</sup> and R<sup>2</sup> are independently selected from lower, meaning C<sub>1-4</sub>, alkyl or hydrogen;

R<sup>3</sup>, R<sup>4</sup>, R<sup>8</sup> and R<sup>9</sup> are independently selected from hydrogen, lower alkyl, lower alkoxy, carbamide, halogen, trifluoromethyl and thio-lower alkyl, with the proviso that R<sup>8</sup> and R<sup>9</sup> cannot both be hydrogen at the same time;

**EP 0 345 808 A1**

A is a C<sub>5-7</sub> cycloalkanyl or cycloalkenyl ring, or  
A is

wherein n is an integer from 1 to 3 and R<sup>5</sup> is the same as R<sup>1</sup>; and  
R<sup>6</sup> and R<sup>7</sup> are independently selected from hydrogen, methyl or R<sup>6</sup> and R<sup>7</sup> can be taken together as a methylene bridge, useful as antidepressants.

## 1-Indolylalkyl-4-(Substituted-Pyridinyl)Piperazines

Background of the Invention

This invention generally pertains to heterocyclic carbon compounds having drug and bio-affecting properties and to their preparation and use. In particular the invention is concerned with 1,4-disubstituted piperazine derivatives wherein one substituent is indol-3-yl-alkyl and the other is a substituted pyridin-2-yl moiety. These compounds possess a unique serotonergic profile that should make them useful in treatment of depression.

Archer disclosed a large series of CNS-depressant indolylalkylpiperazines in U.S. 3,188,313 which issued June 8, 1965. Among the large number of moieties listed for possible substituent selection on the 4-nitrogen atom of the piperazine ring was pyridyl (unsubstituted). In U.S. 3,562,278, issued February 9, 1971, Archer claimed a series of 1-(indol-3-ylethyl)-4-substituted-piperazines having psychomotor depressant activity. Among the possible 4-substituents listed was pyridyl, again unsubstituted.

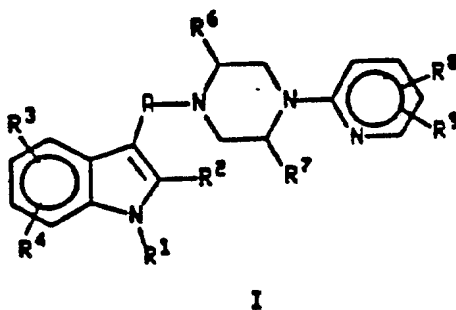
Of less relevance is U.S. 3,472,855, issued October 1969 to Archer, which discloses extension of the series to benz[g]indolyl moieties as replacements for indolyl.

Similarly less relevant is U.S. 4,302,589, issued November 1981 to Fanshawe, et al., which discloses a series of related compounds wherein indoline has replaced the indole moiety. These compounds were disclosed as having antipsychotic properties.

None of the aforementioned references disclose or suggest the 1-indolylalkyl-4-(substituted-pyridinyl)-piperazine derivatives and their antidepressant utility of the present invention.

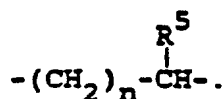
Summary and Detailed Description of the Invention

In its broadest aspect, the present invention is concerned with piperazinyll derivatives having useful antidepressant properties characterized by a compound of Formula I.



In Formula I; R<sup>1</sup> and R<sup>2</sup> are independently selected from hydrogen or lower alkyl. The descriptive term "lower" is used herein to denote an organic radical containing from 1 to 4 carbon atoms. The symbols R<sup>3</sup>, R<sup>4</sup>, R<sup>8</sup> and R<sup>9</sup> refer to moieties which are independently selected from among hydrogen, lower alkyl, lower alkoxy, carboxamide, halogen, trifluoromethyl, and thio-lower alkyl; with the proviso that both R<sup>8</sup> and R<sup>9</sup> cannot be hydrogen at the same time.

The symbol A represents a cycloalkanyl or cycloalkenyl ring comprised of from 5 to 7 carbon atoms. These bridging rings may be 1,2-; 1,3-; or 1,4-disubstituted bridging cycloalkanes or cycloalkenes. In the cycloalkenyl ring the double bond is adjacent to the point of attachment of the 3-indolyl ring. The symbol A can also be the structural fragment:



In this fragment linking the indole and piperazine rings, n is an integer from 1 to 3 and R<sup>5</sup> can be either hydrogen or lower alkyl. The carbon atom to which R<sup>5</sup> is attached is adjacent to the piperazine ring.

Lastly, R<sup>6</sup> and R<sup>7</sup> are independently selected from hydrogen or methyl, or R<sup>6</sup> and R<sup>7</sup> can be taken together as a methylene bridge. Subclasses of compounds envisioned would be: A is cyclic or linear in structure; the piperazine ring is bridged or unbridged. Preferred classes of compounds are those wherein the indolyl and piperazinyl rings are connected by a 2 or 3 carbon linking chain and wherein R<sup>9</sup> is other than hydrogen and is attached to the 6-position of the 2-pyridinyl ring.

Additionally compounds of Formula I also encompass all pharmaceutically acceptable acid addition salts and/or solvates thereof. The present invention is also considered to include stereoisomers as well as optical isomers, e.g. mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds of the instant series. Separation of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

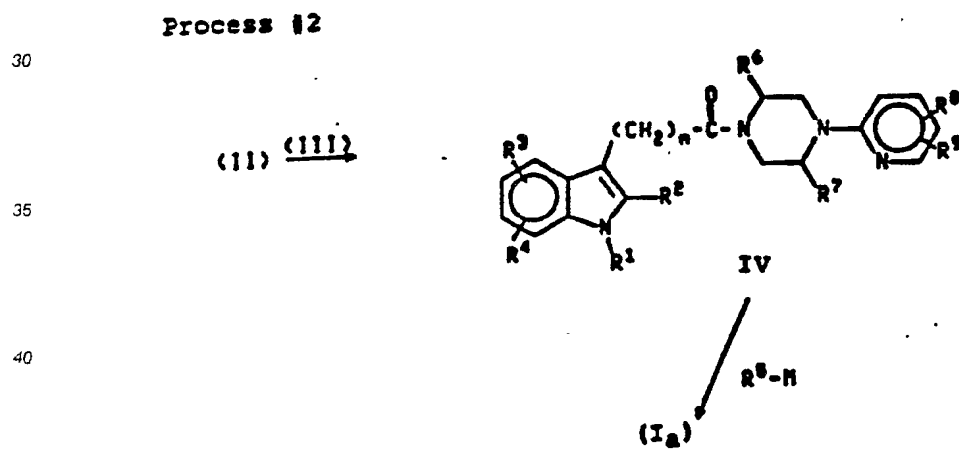
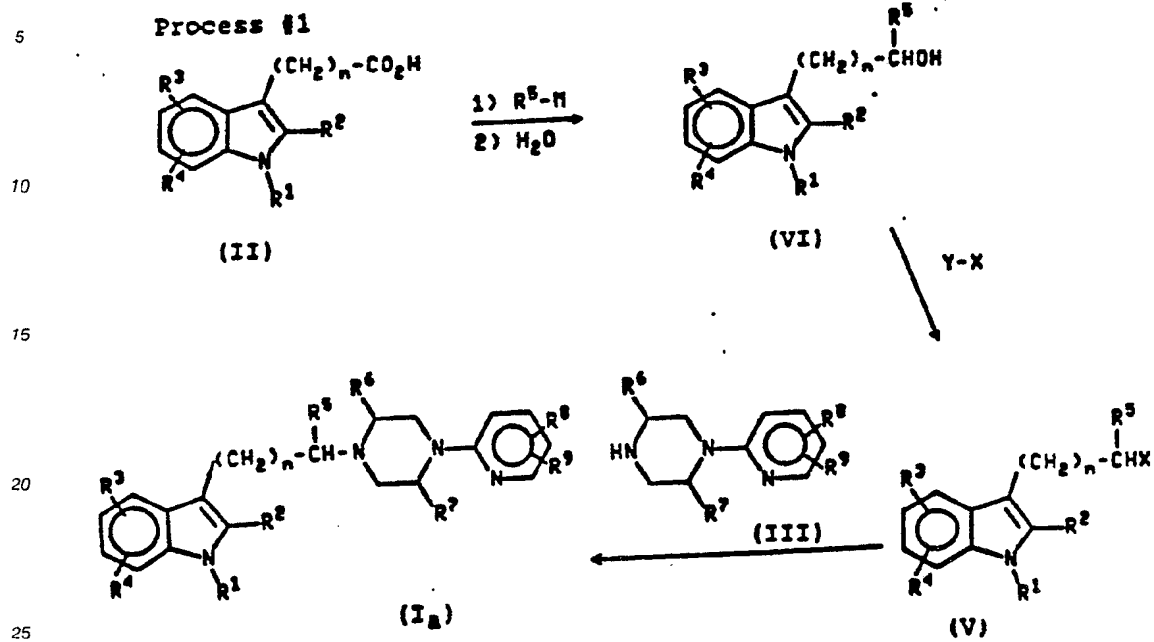
It is to be understood that, as used herein, halogen denotes fluorine, chlorine, bromine and iodine; with the term "lower alkyl" referring to both straight and branched chain carbon radicals of from 1 to 4 carbon atoms inclusive. Illustrative of these radicals are carbon chains which can be methyl, ethyl, propyl, isopropyl, 1-butyl, 1-methylpropyl and 2-methylpropyl. Carboxamide intends a

-  $\begin{array}{c} \text{O} \\ \parallel \\ \text{CNH}_2 \end{array}$  radical.

The pharmaceutically acceptable acid addition salts of the invention are those in which the counter-ion does not contribute significantly to the toxicity or pharmacological activity of the salt and, as such, they are the pharmacological equivalents of the bases of Formula I. They are generally preferred for medical usage. In some instances, they have physical properties which makes them more desirable for pharmaceutical formulation such as solubility, lack of hygroscopicity, compressibility with respect to tablet formation and compatibility with other ingredients with which the substance may be used for pharmaceutical purposes. The salts are routinely made by admixture of a Formula I base with the selected acid preferably by contact in solution employing an excess of commonly inert solvents such as water, ether, benzene, methanol, ethanol, ethyl acetate and acetonitrile. They may also be made by metathesis or treatment with an ion exchange resin under conditions in which the anion of one salt of the substance of the Formula I is replaced by another anion under conditions which allow for separation of the desired species such as by precipitation from solution or extraction into a solvent, or elution from or retention on an ion exchange resin. Pharmaceutically acceptable acids for the purposes of salt formation of the substances of Formula I include sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, cinnamic, mandelic, phosphoric, nitric, mucic, isethionic, palmitic, heptanoic, and others.

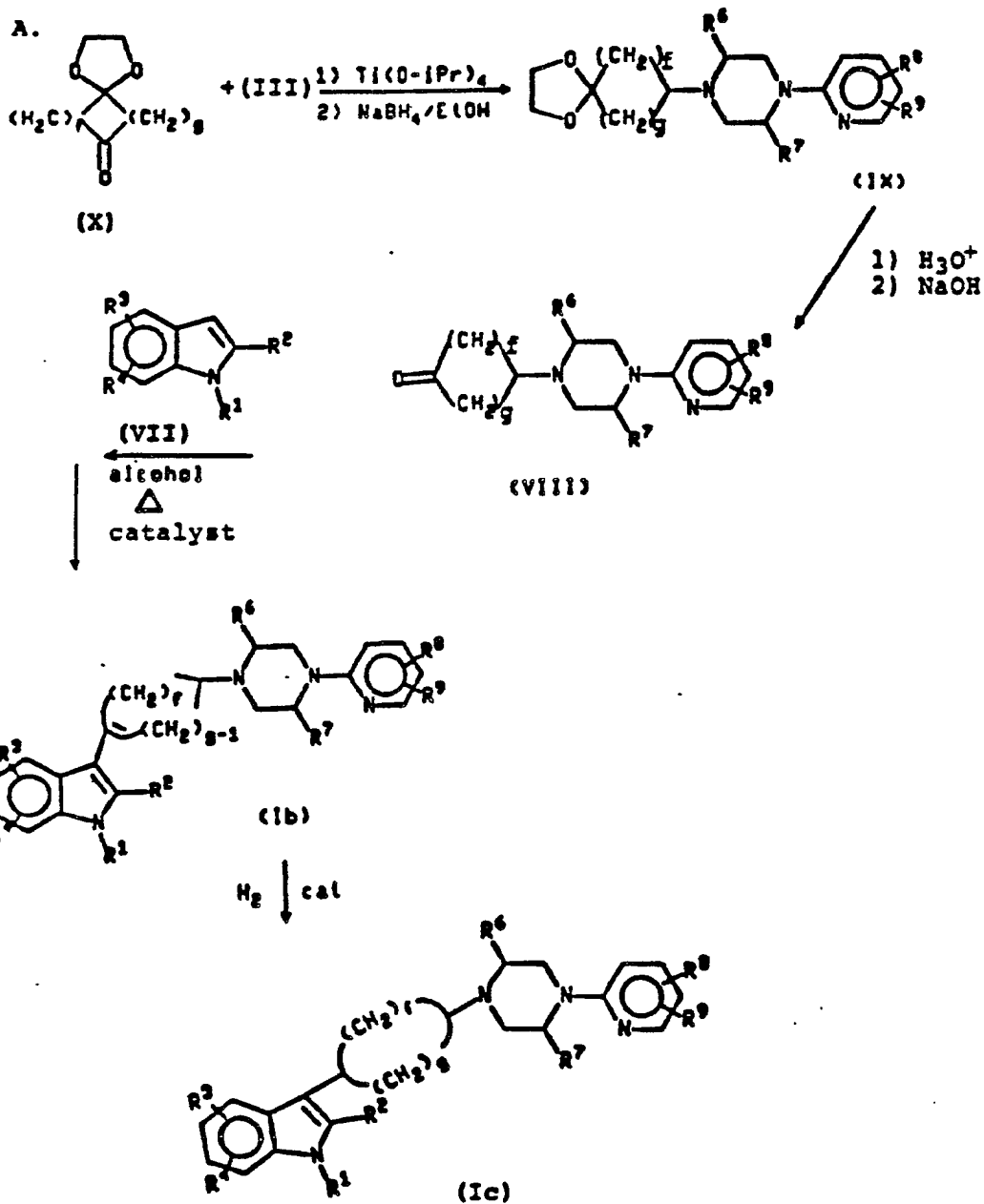
The compounds of Formula I can be prepared by means of the processes shown in Scheme 1.

## Scheme 1



## Scheme 1 (continued)

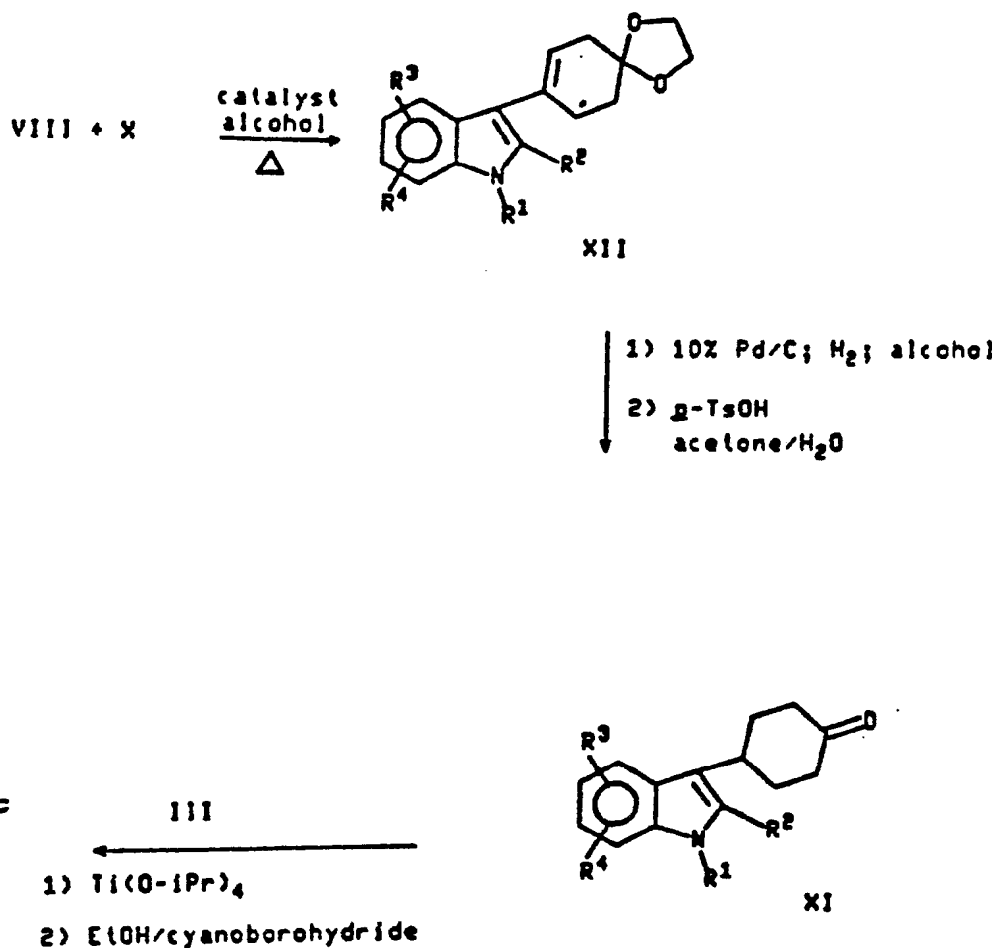
## Process #3



## Scheme 1 (continued)

## Process #3

B.



For the three processes depicted in Scheme 1;  $R^1$  through  $R^5$ , and  $n$  are as defined hereinabove. Additional symbols appearing in Scheme 1 are  $f$ ,  $g$ ,  $M$ ,  $X$  and  $Y$ . The symbols  $f$  and  $g$  are integers from 0 to 5 with the proviso that  $f+g$  must be equal to 3, 4 or 5.  $M$  represents a metalloid species such as magnesium, lithioaluminum, and the like; which, taken with  $R^5$  are either hydride-type reducing agents such as lithium aluminum hydrides, diborane complexes, etc.; or organometallic alkylating agents such as Grignard reagents, etc. The reagent  $Y-X$  represents an organic leaving group reagent wherein  $X$  is the leaving group fragment such as tosyl, mesyl, halide, sulfate, phosphate and so forth; and  $Y$  is either a proton or a counter ion: e.g.  $XY$  can be  $HBr$  or tosyl chloride and the like. These reagents, symbolized by  $R^5-M$  and  $Y-X$ , as well as other reagent acronyms, are familiar to the practitioner skilled in organic synthesis and their structure and usage would be readily understood.

Process #1 in Scheme 1 comprises the following steps:

1) Treatment of an indole carboxylic acid II with  $R^5-M$ , which is either a hydride reducing agent or alkylating agent depending on the selection of  $R^5$  (hydrogen or lower alkyl). This results in generation of the indolyalkanol VI which is a secondary alcohol when  $R^5$  is lower alkyl and a primary alcohol when  $R^5$  is hydrogen.

2) Conversion of the alcohol VI to an organic leaving group (also referred to as a nucleofuge in synthetic organic reaction terminology) by use of an appropriate  $Y-X$  reagent such as  $HBr$  or tosyl chloride to give intermediate V.

3) Displacement of the leaving group anion by the nucleophilic pyridinylpiperazine III to provide the desired product of formula Ia.

Process #2 in Scheme 1 comprises a two-step reaction sequence:

1) Condensation of the indolylcarboxylic acid II with the pyridinylpiperazine III, using standard condensation agents such as acid chlorides, acid anhydrides, dicyclohexylcarbodiimide, and the like, to afford the amide intermediate IV.

2) Treatment of the amide IV with R<sup>5</sup>-M to reductively alkylate or reduce to the desired formula Ia product.

Process #3 in Scheme 1 comprises the following sequence of steps:

A.

1) The pyridinylpiperazine III is reductively alkylated with a cycloalkanedione mono-ethylene ketal X to give the ketal intermediate IX.

2) Deprotecting the ketal IX to produce the cycloalkanone intermediate VIII.

3) Condensing the cycloalkanone VIII with indole VII to yield the cycloalkenyl product Ib which can be catalytically reduced to the cycloalkanyl product Ic if desired.

B.

1) The indole VII, cycloalkanedione mono-ethylene ketal X, and an acid or base catalyst (e.g. pyrrolidine) are refluxed in alcohol to give the condensation product XII.

2) Intermediate XII is catalytically reduced to the saturated cycloalkane ketal which is deketalized to the cycloalkanone intermediate XI.

3) Cycloalkanone XI is condensed with the pyridinylpiperazine III using conditions as shown to yield product Ic.

Reagents, solvents, and reaction conditions for the above described steps of the three processes would be known to one skilled in organic synthesis as all the steps comprise standard organic reactions, the details of which are readily available in the chemical literature. These processes may be adapted to variation in order to produce other compounds embraced by this invention but not specifically disclosed. Variations of the methods to produce the same compounds in somewhat different fashion will also be evident to one skilled in the art. As example of this, VI intermediate compounds wherein n is 1 are conveniently prepared by treating various substituted 3-indoleglyoxylic acid esters with LiAlH<sub>4</sub>.

To provide greater descriptive details, representative synthetic examples are provided hereinbelow in the "Description of Specific Embodiments" section. Similarly, preparations of starting intermediate compounds such as II and III, while readily available in the chemical literature, are also described using specific examples in that section of the patent specification.

The compounds comprising the present invention inhibit the re-uptake of endogenous serotonin. Selective inhibitors of serotonin uptake are effective for the treatment of mental depression and have been reported to be useful for treating chronic pain (see: R.W. Fuller, "Pharmacologic Modification of Serotonergic Function: Drugs for the Study and Treatment of Psychiatric and Other Disorders", *J. Clin. Psychiatry* 47:4 (Suppl.) April 1986, pp. 4-8). Compounds of the present invention are also envisioned to be useful in the following disorders: obsessive-compulsive disorder, feeding disorders, anxiety disorders and panic disorders.

Additionally, selected compounds of the invention potently inhibit norepinephrine re-uptake and blockade of endogenous norepinephrine re-uptake is also a mechanism through which it is believed that various antidepressant agents exert their therapeutic effect (see: "Antidepressants: Neurochemical, Behavioral, and Clinical Perspectives", edited by S.J. Enna, J.B. Mallick and E. Richardson, (1981), Raven Press, New York, pp. 1-12).

Determination of endogenous monoaminergic re-uptake inhibition values both for serotonin and norepinephrine was accomplished using test methods described by P. Skolnick, et al., *Br. J. Pharmacology* (1985), 86, pp. 637-644; with only minor modifications. *In vitro* IC<sub>50</sub> (nM) test values were determined for representative compounds of Formula I based on their inhibition of synaptosomal reuptake of tritiated serotonin. Test data IC<sub>50</sub> values lower than 500nM are considered to reflect activity as an inhibitor of serotonin reuptake. Compounds with IC<sub>50</sub> values lower than 100nM comprise preferred compounds.

Another aspect of the instant invention provides a method for treating a mammal afflicted with depression or chronic pain which comprises administering systemically to said mammal a therapeutically



effective amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof.

The administration and dosage regimen of compounds of Formula I is considered to be done in the same manner as for the reference compound fluoxetine, cf: Schatzberg, et al., *J. Clin. Psychopharmacology* 7 6 Suppl. (1987) pp. 445-495, and references therein. Although the dosage and dosage regimen must in each case be carefully adjusted, utilizing sound professional judgment and considering the age, weight and condition of the recipient, the route of administration and the nature and gravity of the illness, generally the daily dose will be from about 0.05 to about 10 mg/kg, preferably 0.1 to 2 mg/kg, when administered parenterally and from about 1 to about 50 mg/kg, preferably about 5 to 20 mg/kg, when administered orally. In some instances, a sufficient therapeutic effect can be obtained at lower doses while in others, larger doses will be required. Systemic administration refers to oral, rectal and parenteral (i.e. intramuscular, intravenous and subcutaneous). Generally, it will be found that when a compound of the present invention is administered orally, a larger quantity of the active agent is required to produce the same effect as a similar quantity given parenterally. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce effective antidepressant effects without causing any harmful or untoward side effects.

The compounds of the present invention may be administered for antidepressant purposes either as individual therapeutic agents or as mixtures with other therapeutic agents. Therapeutically, they are generally given as pharmaceutical compositions comprised of an antidepressant amount of a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Pharmaceutical compositions which provide from about 1 to 500 mg of the active ingredient per unit dose are preferred and are conventionally prepared as tablets, lozenges, capsules, powders, aqueous or oily suspensions, syrups, elixirs, and aqueous solutions.

The nature of the pharmaceutical composition employed will, of course, depend on the desired route of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g. starch) and wetting agents (e.g. sodium lauryl sulfate). Solutions or suspensions of a Formula I compound with conventional pharmaceutical vehicles are employed for parenteral compositions such as an aqueous solution for intravenous injection or an oily suspension for intramuscular injection.

### Description of Specific Embodiments

The compounds which constitute this invention, their methods of preparation and their biologic actions will appear more fully from consideration of the following examples, which are given for the purpose of illustration only and are not to be construed as limiting the invention in sphere or scope. In the following examples, used to illustrate the foregoing synthetic processes, temperatures are expressed in degrees Celsius and melting points are uncorrected. The nuclear magnetic resonances (NMR) spectral characteristics refer to chemical shifts ( $\delta$ ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the <sup>1</sup>H NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m) or doublet (d). Abbreviations employed are DMSO-d<sub>6</sub> (deuterodimethylsulfoxide), CDCl<sub>3</sub> (deuteriochloroform) and are otherwise conventional. The infrared (IR) spectral descriptions include only absorption wave numbers (cm<sup>-1</sup>) having functional group identification value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight and are given in Table 3.

The following examples describe in detail the preparation of compounds of Formula I, as well as synthetic intermediates in each process. It will be apparent to those skilled in the art that modifications, both of materials and methods, will allow preparation of other compounds disclosed herein. From the foregoing description and the following examples it is believed that one skilled in the art is able to use the invention to the fullest extent.

#### A. Preparation of Intermediate Compounds

Some representative procedures for preparation of synthetic intermediate compounds utilized in the three processes of Scheme 1 are given hereinbelow. Most starting materials and certain intermediates (e.g. Formula II and VII compounds), are either commercially available or procedures for their synthesis are readily available in the chemical literature allowing their full utilization by one skilled in the art of organic

synthetic chemistry.

### Compounds of Formula III

#### Example 1

##### 1-(3-Methoxy-2-pyridinyl)piperazine

To a stirred mixture of 2-bromo-3-pyridinol (71.0 g) and pulverized KOH (77.8 g) in DMSO (500 mL) at 15 55-60 °C and under N<sub>2</sub> atmosphere was added dropwise a solution of CH<sub>3</sub>I (72.4 g) in DMSO (100 mL). After the addition was complete, the reaction was maintained at 55-60 °C for ½ h. The mixture was then poured into ice water (800 g) and the precipitate filtered. The precipitate was triturated with Et<sub>2</sub>O (3 x 500 mL) and the combined extracts treated in turn with 1 N NaOH (500 mL), water (500 mL), 1 N HCl (3 x 250 mL), and sat. NaCl solution (500 mL). The organic phase was dried with anhydrous MgSO<sub>4</sub>, filtered, and 20 concentrated under reduced pressure to afford 2-bromo-3-methoxypyridine (52.3 g; 68%).

Anhydrous piperazine (45.6 g) and 2-bromo-3-methoxy-pyridine (10.0 g) were heated neat in an autoclave at 100 °C for 20 h. Upon cooling, the mixture was treated with 5% NaCO<sub>3</sub> (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The extracts were dried using anhydrous K<sub>2</sub>CO<sub>3</sub>, filtered, and concentrated under reduced pressure to yield 1-(3-methoxy-2-pyridinyl)piperazine (III; 8.43 g; 82%) after silica gel chromatog- 25 raphy (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH; 93:7:0.7).

#### Example 2

##### 1-(3-Trifluoromethyl-2-pyridinyl)piperazine

A mixture of 2-chloro-3-trifluoromethyl pyridine (5.0 g), anhydrous piperazine (7.22 g), and micropul- 35 verized anhydrous K<sub>2</sub>CO<sub>3</sub> (7.73 g) in acetonitrile (50 mL) was heated at reflux with stirring while under N<sub>2</sub> atmosphere for 20 h. The excess acetonitrile was removed under reduced pressure and water (15 mL) added to the concentrate. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with sat. NaCl solution, dried with anhydrous MgSO<sub>4</sub>, and concentrated under 40 reduced pressure. Silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH; 94:6:0.6) of the residue yielded 1-(3-trifluoromethyl-2-pyridinyl)piperazine (III; 5.50 g; 85%).

#### Example 3

##### 1-(6-Methoxy-2-pyridinyl)piperazine

A mixture of 1-(6-chloro-2-pyridinyl)piperazine (6.0 g) and NaOMe (16.42 g) in DMF (25 mL) was heated 50 at 100 °C under nitrogen atmosphere for 20 h. The excess DMF was then removed under reduced pressure. Water (5 mL) was added to the residue and the mixture extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with sat. NaCl solution, dried with anhydrous MgSO<sub>4</sub>, filtered and concentrated 55 under reduced pressure. Silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 98:2) of the concentrate yielded the 4-(6-methoxy-2-pyridinyl)-1-piperazinecarboxaldehyde (5.13 g; 81%).

A mixture of the formamide intermediate, prepared above, (3.55 g) in 6 N HCl (30 mL) was heated at reflux for ½ h. The reaction was cooled to 0 °C, made basic with 10 N NaOH, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3

x 50 mL). The combined organic layers were washed with sat. NaCl solution, dried with anhydrous  $K_2CO_3$ , filtered, and concentrated under reduced pressure to afford 1-(6-methoxy-2-pyridinyl)piperazine (2.72 g; 83%).

5

## Example 4

10

1-(6-Chloro-2-pyridinyl)piperazine

A mixture of 2,6-dichloropyridine (4.0 g), anhydrous piperazine (6.97 g), and micropulverized anhydrous  $K_2CO_3$  (7.45 g) in acetonitrile (50 ml) was heated at reflux with stirring while under  $N_2$  atmosphere for 20 h. The excess acetonitrile was removed under reduced pressure and water (15 mL) added to the concentrate. The aqueous phase was extracted with  $CH_2Cl_2$  (3 x 50 mL). The combined  $CH_2Cl_2$  extracts were washed with sat. NaCl solution, dried with anhydrous  $MgSO_4$ , and concentrated under reduced pressure. Silica gel chromatography ( $CH_2Cl_2$ /MeOH/ $NH_4OH$ ; 94:6:0.6) of the residue yielded 1-(6-chloro-2-pyridinyl)piperazine (4.80 g; 90%).

20

## Example 5

25

2-(3-Methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptaneA. Preparation of (1S,4S)-N-Benzyl-2,5-diazabicyclo[2.2.1]heptane

30

(cf: J. Org. Chem. (1966), 31, 1059-1062)

1) N-Tosylhydroxy-L-proline

35

To a solution of hydroxy-L-proline (80 g) in 2N NaOH (800 mL) was added tosyl chloride (136.1 g) in  $Et_2O$  (700 mL). The reaction mixture was stirred at  $0^\circ C$  for  $1\frac{1}{2}$  h and continued for an additional  $3\frac{1}{2}$  h at  $23^\circ C$ . The aqueous layer was separated, acidified with concentrated HCl to pH 1 and allowed to stand at  $-10^\circ C$  for 12 h. The precipitate was filtered, washed with cold water, and concentrated in vacuo to a volume of 300 mL. The precipitate obtained was combined with the previous precipitate. The combined solids were recrystallized from ethyl acetate. Drying in vacuo at  $50^\circ C$  for 24 h afforded trans-4-hydroxy-1-(4-toluenesulfonyl)-L-proline (107.38 g, 62%).

40

## 2) Potassium salt of trans-4-hydroxy-1-(4-toluenesulfonyl)-L-proline

45

To a solution of trans-4-hydroxy-1-(4-toluenesulfonyl)-L-proline (107.38 g) in acetone (450 mL) was added potassium 2-ethyl hexanoate in BuOH (1.91 N; 189.5 mL). After standing at  $23^\circ C$  for 20 min, the insoluble material was filtered and the resulting solution was concentrated to 320 mL.  $Et_2O$  (1000 mL) was added to the concentrate and the solvents removed under reduced pressure yielding a solid (122.90 g). The hygroscopic product was used in the next step without further purification.

50

3) N-Tosylhydroxy-L-proline methyl ester

55

To a solution of potassium trans-4-hydroxy-1-(4-toluenesulfonyl)-L-proline (122.90 g) in 250 mL of N,N-dimethylacetamide was added methyl iodide (24.5 mL) while under nitrogen atmosphere. The light protected mixture was stirred 16 h. The mixture was poured onto ice water and extracted with  $CH_2Cl_2$  (3 x 400 mL). The combined organic extracts were washed with 2%  $NaHCO_3$  (400 mL),  $H_2O$  (4 x 1.5 L), dried

over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to leave a viscous oil. The crude oil was triturated within petroleum ether to give N-tosylhydroxy-L-proline methyl ester as a pale yellow solid (63.20 g, 56.2%) which was used in the next step without further purification.

5 4) (2S,4R)-1-(4-toluenesulfonyl)-2-hydroxymethyl-4-hydroxy pyrrolidine

To a solution of N-tosylhydroxy-L-proline methyl ester (62.20 g) in THF (600 mL) at  $0^\circ\text{C}$  for 1 h and allowed to stand at  $23^\circ\text{C}$  for 18 h. The reaction mixture was cooled to  $-20^\circ\text{C}$ , made neutral with 6N HCl, and concentrated under reduced pressure. The residue was treated with water (550 mL) and extracted with EtOAc (4 x 300 mL). The combined organic extracts were washed with  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to give N-tosylhydroxy-L-prolinol as a white solid (50.56 g, 88.8%) which was used in the next step without further purification.

15 5) (2S,4R)-1-(4-toluenesulfonyl)-2-(4-toluenesulfonyloxymethyl)-4-(4-toluenesulfonyloxy)-pyrrolidine

To a solution of p-toluenesulfonyl chloride (155 g) in pyridine (330 mL) at  $0^\circ\text{C}$  was added N-tosylhydroxy-L-prolinol (104.40 g). The reaction mixture was kept at  $6^\circ\text{C}$  for 72 h and then poured into cold 2N HCl (2.5 L). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 1000 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to give an oil. The oil was triturated with EtOH and the solid that formed was collected by filtration. The crude product was recrystallized from EtOH (3.5 L) to give tritosylhydroxy-L-prolinol (99.87 g, 44.2%, m.p.  $130\text{--}132^\circ\text{C}$ ,  $[\alpha]_{\text{D}}^{24} = -57.1$ , c = 1.2, acetone).

25 6) (1S,4S)-2-(4-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicyclo[2.2.1]heptane

To a suspension of tritosylhydroxy-L-prolinol (99.87 g) in toluene (350 mL) was added benzylamine (54.83 g). The resulting mixture was heated at reflux for 18 h and allowed to cool at  $23^\circ\text{C}$ . The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was triturated with ethanol and the solid that formed was collected by filtration to give (1S,4S)-2-(4-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicycloheptane (54.18 g, 93.2%) which was used in the next step without further purification.

35 7) (1S,4S)-N-benzyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide

A mixture of (1S,4S)-2-(4-toluenesulfonyl)-5-phenylmethyl-2,5-diazabicyclo[2.2.1]heptane (54.0 g) in acetic acid (830 mL) containing hydrobromic acid (30% wt) was heated at  $70^\circ\text{C}$  for 18 h. The reaction mixture was allowed to cool and concentrated under reduced pressure to a final volume of ca. 300 mL. The precipitate that formed was filtered and washed with acetone to give (1S,4S)-N-benzyl-2,5-diazabicyclo[2.2.1]heptane (50.30 g 91.3%, m.p.  $272\text{--}275^\circ\text{C}$ ).

By adjusting the starting materials and using the foregoing synthetic scheme the other isomer, (1R,4R)-N-benzyl-2,5-diazabicyclo[2.2.1]heptane can be obtained (cf: J. Org. Chem. (1981), 46 2954-2960).

B. 2-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane

50 1) 2-(3-methoxy-2-pyridinyl)-5-phenylmethyl-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane

A mixture of 2-bromo-3-methoxy pyridine (9.9 g) and (1S,4S)-N-benzyl-2,5-diazabicyclo[2.2.1]heptane (10.9 g) was heated at  $100^\circ\text{C}$  in a Parr bomb for 67 h. The reaction mixture was cooled to  $23^\circ\text{C}$ , dissolved in  $\text{CH}_2\text{Cl}_2$ , extracted with 5%  $\text{NaHCO}_3$ , and finally with  $\text{H}_2\text{O}$ . The organic layer was dried over  $\text{K}_2\text{CO}_3$ , filtered, and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2\text{:MeOH}$ ; 96:4) to give the desired produce (7.93 g, 51%).

## 2) 2-(3-methoxy-2-pyridinyl)-5-phenylmethyl-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane

(7.88 g) in EtOH (250 mL) was acidified to a pH of 1 with ethanolic HCl. The reaction mixture was treated with 5% palladium-on-carbon (2.05 g) and hydrogenated at 50 psi at 60 °C for 6 h. After this time, the heating was discontinued and the reaction mixture was allowed to cool to room temperature and the hydrogenation continued for 16 h. The reaction mixture was filtered through celite. The filtrate was concentrated under reduced pressure and the residue was made alkaline by the addition of 5N NaOH. The solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 250 mL) and combined CH<sub>2</sub>Cl<sub>2</sub> extracts were dried over K<sub>2</sub>CO<sub>3</sub>, filtered, and concentrated under reduced pressure to give 2-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane (4.67 g; 85.2%).

Compounds of Formula IV

## Example 6

1-[4-(1H-indol-3-yl)-1-oxobutyl]-4-(3-methoxy-2-pyridinyl)piperazine

To a mixture of 1-(3-methoxy-2-pyridinyl)piperazine (III; 1.28 g), 3-indolebutyric acid (1.08 g), and triethylamine (1.02 g) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added 1-methyl-2-chloro-pyridinium iodide (1.62 g). The reaction was heated at reflux with stirring and under N<sub>2</sub> atmosphere for 4 h. After cooling to ambient temperature, the solution was extracted with aqueous 5% HCl followed by aqueous 5% NaHCO<sub>3</sub>. The organic phase was dried with anhydrous K<sub>2</sub>CO<sub>3</sub>, filtered, and concentrated under reduced pressure. Silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH; 98:2) of the concentrate afforded the amide product (IV; 1.00 g; 50%).

Compounds of Formula V

## Example 7

3-(3-bromopropyl)-1H-indole

Phosphorus tribromide (17.4 g) in Et<sub>2</sub>O (30 mL) was added dropwise to a Et<sub>2</sub>O solution (100 mL) containing 3-(3-hydroxypropyl)indole (VI; 7.5 g) at 0 °C with stirring and under N<sub>2</sub> atmosphere. After the addition was complete, the reaction was allowed to warm to 23 °C and continuously stirred for 16 h. At the end of this time, the reaction was cooled to 0 °C and ice (ca. 25 mL) added portionwise and stirred an additional 2 h. The organic phase was separated from the aqueous phase and the aqueous layer extracted with Et<sub>2</sub>O. The combined organic phases were washed with sat. NaCl solution, dried with MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford 3-(3-bromopropyl)indole (V; 1.51 g; 15%).

## Example 8

5-Fluoro-3-(2-bromoethyl)indole

To a solution of 5-fluoro-3-(2-hydroxyethyl)indole (10.3 g, 0.056 mol) and CBr<sub>4</sub> (24.8 g, 0.073 mol) in 100 mL of dry acetonitrile at 0 °C under Ar was added a solution of triphenylphosphine (19.6 g, 0.073 mol) in 200 mL of dry acetonitrile. The mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The resulting mixture was evaporated and the residue was chromatographed (SiO<sub>2</sub>/ethyl acetate-hexane =

1:4) to give the produce (8.50 g, 61%) as a brown solid;  
 IR (neat)  $3440\text{ cm}^{-1}$ ;  
 $^1\text{Hnmr}$  (80 MHz,  $\text{CDCl}_3$ )  
 $\delta$ : 7.75 (br s, 1H), 7.15-6.57 (m, 4H), 3.53-3.32 (m, 2H), 3.17-2.94 (m, 2H).

#### Compounds of Formula VI

#### Example 9

##### 3-(3-hydroxypropyl)-1H-indole

To a stirred suspension of  $\text{LiAlH}_4$  (4.02 g) in THF (200 mL) at  $0^\circ\text{C}$  and under  $\text{N}_2$  atmosphere was added dropwise a THF solution (100 mL) containing indole-3-propanoic acid (20.0 g). After the addition was complete, the reaction was heated at reflux for 16 h, after which time the mixture was cooled to  $0^\circ\text{C}$  and water (4 mL) added, followed by 15%  $\text{NaOH}$  (4 mL), and finally additional water (12 mL). The reaction was filtered and the THF filtrate extracted with 5%  $\text{NaOH}$  (4 mL), and finally additional water (12 mL). The reaction was filtered and the THF filtrate extracted with 5%  $\text{NaHCO}_3$  followed by a sat.  $\text{NaCl}$  solution. The organic phase was dried with anhydrous  $\text{K}_2\text{CO}_3$ , filtered, and concentrated under reduced pressure to yield 3-(3-hydroxypropyl)indole (VI; 7.5 g; 41%).

#### Example 10

##### 3-(2-hydroxyethyl)-1H-indole

To a stirred suspension of  $\text{LiAlH}_4$  (3.24 g) in THF (200 mL) at  $0^\circ\text{C}$  and under  $\text{N}_2$  atmosphere was added dropwise a THF solution (50 mL) containing indole-3-acetic acid (10.0 g). After the addition was complete, the reaction was heated at reflux for 3 h, after which time the mixture was cooled to  $0^\circ\text{C}$  and water (3.3 mL) added, followed by 15%  $\text{NaOH}$  (3.3 mL), and finally additional water (9.9 mL). The reaction was filtered and the filter cake washed with  $\text{Et}_2\text{O}$ . The organic layers were combined, dried with anhydrous  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to yield 3-(2-hydroxyethyl)indole (VI; 7.4 g; 80%).

#### Example 11

##### 5-Fluoro-3-(2-hydroxyethyl)indole

To a suspension of  $\text{LiAlH}_4$  (8.60 g, 0.23 mol) in 400 mL of dry THF was added 5-fluoro-3-indoleglyoxylic acid ethyl ester (13.50 g, 0.057 mol) portionwise at room temperature. Preparation of this ester intermediate is given hereinbelow. The mixture was heated to reflux under Ar for 1 h and was then cooled at  $0^\circ\text{C}$  and quenched according to the method of Fieser (Fieser and Fieser, "Reagents for Organic Synthesis", Vol. 1 pg. 584). The resulting slurry was filtered and the filter cake was washed with THF. The filtrate was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give the produce (10.00 g, 100%) as a yellow oil. It was used as such without further purification;  
 IR (neat)  $3420\text{ cm}^{-1}$   
 $^1\text{Hnmr}$  (80 MHz,  $\text{CDCl}_3$ )

$\delta$ : 7.73 (br s, 1H), 7.1-6.4 (m, 4H), 3.57 (t, J = 8 Hz, 2H), 2.66 (t, J = 8 Hz, 2H), 1.20 (br s, 1H).

#### 5-Fluoro-3-indoleglyoxylic acid ethyl ester

5

To a solution of 5-fluoroindole (7.35 g, 0.054 mol) in 75 mL of anhydrous ether was added oxalyl chloride (5.60 mL, 0.064 mol) dropwise at 0 °C under Ar.

The yellow suspension was stirred at 0 °C for 1½ h and then the solid was collected by filtration and  
 10 dried in vacuo to give 5-fluoro-3-indoleglyoxylyl chloride (12.0 g, 100%) as a yellow solid; IR (neat) 1765, 1627 cm<sup>-1</sup>.

This solid was taken up in 160 mL of absolute ethanol and was then treated with triethylamine (8.1 mL, 0.058 mol) dropwise at 0 °C under Ar. The mixture was refluxed for 4½ h and was then allowed to cool to room temperature. The resulting precipitate was filtered and then dried in vacuo to give the produce (10.8  
 15 g, 87%) as a yellow solid which was used without further purification.

#### Compounds of Formula VIII

20

#### Example 12

#### 25 4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-cyclohexan-1-one

A solution of 4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-cyclohexan-1-one ethylene ketal (IX, Example 11: 7.56 g, 22 mmole) in 10% aqueous HCl (200 mL) was refluxed for 16 h. The solution was cooled and then neutralized with 30% aqueous NaOH solution. The mixture was then extracted with ethyl acetate (3 x 75  
 30 mL) and the extracts were dried over Na<sub>2</sub>CO<sub>3</sub>. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate as the eluent to give the desired ketone product (VIII) as an oil (5.70 g, 92%).

#### 35 Compounds of Formula IX

#### Example 13

40

#### 4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-cyclohexan-1-one ethylene ketal

A solution of 1-(6-chloro-2-pyridinyl)-piperazine (8.00 g, 40 mmole), 1,4-cyclohexanedione mono-  
 45 ethylene ketal (6.25 g, 40 mmole), and titanium(IV) isopropoxide (15 mL, 14.21 g, 50 mmole) was heated to 80 °C for 30 min. The mixture was cooled and diluted with absolute ethanol (40 mL). Sodium borohydride (ten 0.4 g tablets, 0.1 mole) was added and the mixture was stirred for 4 h. Water (10 mL) was added to the solution with stirring and the solid titanium dioxide was filtered off. The filtrate was concentrated in vacuo  
 50 and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (75 mL). The solution was again filtered and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate as the eluent to give the desired ketal produce (IX) as an oil (7.56 g, 56%).

#### B. Preparation of Formula I Products

55

#### By Process 1 (Ia Products)

## Example 14

5 4-[6-Chloro-2-pyridinyl]-1-[2-(1H-indol-3-yl)-ethyl]-piperazine hydrochloride

A mixture of 3-(2-bromoethyl)indole (2.05 g), 1-(6-chloro-2-pyridinyl)piperazine (3.61 g), micropulverized  $K_2CO_3$  (2.52 g) and tetrabutylammonium hydrogen sulfate (0.16 g) in acetonitrile (25 mL) was heated at reflux under  $N_2$  atmosphere for  $2\frac{1}{2}$  h. The excess acetonitrile was removed under reduced pressure and water (15 mL) added to the concentrate. The aqueous phase was extracted with  $CH_2Cl_2$  (3 x 50 mL). The combined  $CH_2Cl_2$  extracts were washed with sat. NaCl solution, dried with anhydrous  $K_2CO_3$ , and concentrated under reduced pressure. Silica gel chromatography (EtOAc/Hexanes; 70:30) of the residue yielded the free base (3.10 g; 99%) which was treated with ethanolic HCl to provide the desired Ia product (2.63 g; 77%).

Anal. Calcd. for $C_{19}H_{21}N_4Cl \cdot HCl$ :			
	C, 60.49;	H, 5.88;	H, 14.85
found:	C, 60.27;	H, 5.88;	N, 14.66

NMR ( $DMSO-d_6$ ): 3.24 (8H, m); 3.72 (2H, m); 4.40 (2H, m); 6.81 (1, d, 7.4 Hz); 7.02 (3H, m); 7.25 (1H, d, 1.0 Hz); 7.39 (1H, m); 7.64 (2H, m); 10.85 (1H, bs); 10.98 (1H, bs).  
IR (KBr): 750, 770, 960, 1140, 1270, 1420, 1460, 1550, 1600, 2440 and  $3240\text{ cm}^{-1}$ .

## Example 15

30 1-[2-(1H-indol-3-yl)-ethyl]-4-[6-trifluoromethyl-2-pyridinyl]piperazine hydrochloride

A mixture of 3-(1-bromoethyl)indole (1.12 g), 1-(6-trifluoromethyl-2-pyridinyl)piperazine (2.31 g), micropulverized  $K_2CO_3$  (1.38 g) and tetrabutylammonium hydrogen sulfate (0.08 g) in acetonitrile (50 mL) was heated at reflux under  $N_2$  atmosphere for  $2\frac{1}{2}$  h. The excess acetonitrile was removed under reduced pressure and water (10 mL) added to the concentrate. The aqueous phase was extracted with  $CH_2Cl_2$  (3 x 50 mL). The combined  $CH_2Cl_2$  extracts were washed with sat. NaCl solution, dried with anhydrous  $K_2CO_3$ , and concentrated under reduced pressure. Silica gel chromatography ( $CH_2Cl_2$ /MeOH; 98:2) of the residue yielded the free base (1.56 g; 83%) which was treated with ethanolic HCl to yield the hydrochloride salt of the desired Ia product (1.17 g; 68%).

Anal. Calcd. for $C_{20}H_{21}N_4F_3 \cdot HCl$ :			
	C, 58.47;	H, 5.40;	N, 13.64
Found:	C, 58.37;	H, 5.38;	N, 13.56.

NMR ( $DMSO-d_6$ ): 3.25 (8H, m); 3.72 (2H, d, 13.4 Hz); 4.48 (2H, d, 13.4 Hz); 7.10 (5H, m); 7.34 (1H, d, 7.0 Hz); 7.61 (1H, d, 7.0 Hz); 7.83 (1H, m); 10.60 (1H, bs); 10.95 (1H, bs).  
IR (KBr): 740, 800, 960, 1120, 1130, 1340, 1490, 1610, 2600, 2925 and  $3250\text{ cm}^{-1}$ .

## Example 16

55 1-[2-(1H-indol-3-yl)-ethyl]-4-[6-methoxy-2-pyridinyl]piperazine hydrate

A mixture of 3-(2-bromoethyl)indole (1.66 g), 1-(6-methoxy-2-pyridinyl)piperazine (2.86 g), micropul-



verized  $K_2CO_3$  (2.04 g) and tetrabutylammonium hydrogen sulfate (0.13 g) in acetonitrile (50 mL) was heated at reflux under  $N_2$  atmosphere for 2 h. The excess acetonitrile was removed under reduced pressure and water (10 mL) added to the concentrate. The aqueous phase was extracted with  $CH_2Cl_2$  (3 x 50 mL). The combined  $CH_2Cl_2$  extracts were washed with sat. NaCl solution, dried with anhydrous  $K_2CO_3$ , and concentrated under reduced pressure. Silica gel chromatography ( $CH_2Cl_2/MeOH$ ; 96:4) of the residue yielded the free base of the desired Ia product (2.20 g; 89%).

Anal. Calcd. for $C_{20}H_{24}N_4O \cdot 0.5 C_2H_5O \cdot 0.5 H_2O$ :				
	C, 68.46;	H, 7.66;	N, 15.21;	$H_2O$ , 2.45
Found:	C, 68.24;	H, 7.59;	N, 15.35;	$H_2O$ , 2.30.

NMR ( $CDCl_3$ ): 2.70 (6H, m); 3.08 (2H, m); 3.61 (4H, m); 3.90 (3H, s); 6.11 (1H, d, 9.5 Hz); 6.20 (1H, d, 9.0 Hz); 7.12 (3H, m); 7.40 (2H, m); 7.68 (1H, m); 8.00 (1H, bs).  
IR (KBr): 745, 790, 985, 1250, 1450, 1460, 1590, 2840, 3180 and  $3550\text{ cm}^{-1}$ .

#### Example 17

##### 1-[2-(1H-indol-3-yl)-ethyl]-4-[3-trifluoromethyl-2-pyridinyl]piperazine hydrochloride

A mixture of 3-(2-bromoethyl)indole (1.79 g), 1-(3-trifluoromethyl-2-pyridinyl)piperazine (1.85 g), micro-pulverized  $K_2CO_3$  (2.21 g) and tetrabutylammonium hydrogen sulfate (.014 g) in acetonitrile (50 mL) was heated at reflux under  $N_2$  atmosphere for 3 h. The excess acetonitrile was removed under reduced pressure and water (10 mL) added to the concentrate. The aqueous phase was extracted with  $CH_2Cl_2$  (3 x 50 mL). The combined  $CH_2Cl_2$  extracts were washed with sat. NaCl solution, dried with anhydrous  $K_2CO_3$ , and concentrated under reduced pressure. Silica gel chromatography ( $CH_2Cl_2/MeOH$ ; 97:3) of the residue yielded the free base (1.66 g; 56%) which was treated with ethanolic HCl to yield the hydrochloride salt of the desired Ia product (1.45 g; 80%).

Anal. Calcd. for $C_{20}H_{22}N_4F_3 \cdot HCl$ :			
	C, 58.47;	H, 5.40;	N, 13.64
Found:	C, 58.60;	H, 5.43;	N, 13.66.

NMR ( $DMSO-d_6$ ): 3.30 (10H, m); 3.72 (2H, m); 7.08 (2H, m); 7.22 (1H, d, 4.9 Hz); 7.35 (2H, m); 7.66 (1H, m); 8.12 (1H, m); 8.60 (1H, m).  
IR (KBr): 750, 1040, 1130, 1320, 1450, 1580, 1595, 2460, 2580 and  $3230\text{ cm}^{-1}$ .

#### Example 18

##### 1-[2-(1H-indol-3-yl)-ethyl]-4-[3-methoxy-2-pyridinyl]piperazine

A mixture of 3-(2-bromoethyl)indole (2.00 g), 1-(3-methoxy-2-pyridinyl)piperazine (1.72 g), micropulverized  $K_2CO_3$  (2.46 g) and tetrabutylammonium hydrogen sulfate (0.15 g), in acetonitrile (50 mL) was heated at reflux under  $N_2$  atmosphere for 5 h. The excess acetonitrile was removed under reduced pressure and water (10 mL) was added to the concentrate. The aqueous phase was extracted with  $CH_2Cl_2$  (3 x 50 mL). The combined  $CH_2Cl_2$  extracts were washed with sat. NaCl solution, dried with anhydrous  $K_2CO_3$ , and concentrated under reduced pressure. Silica gel chromatography ( $CH_2Cl_2/MeOH$ ; 96:4) of the residue yielded the free base of the desired Ia product (1.32 g; 44%).

Anal. Calcd. for C <sub>20</sub> H <sub>24</sub> N <sub>4</sub> O:			
	C, 71.41;	H, 7.20;	N, 16.66
Found:	C, 71.34;	H, 7.23;	N, 16.55.

NMR (CDCl<sub>3</sub>): 2.80 (6H, m); 3.04 (2H, m); 3.55 (4H, m); 3.90 (3H, s); 6.86 (1H, dd, 4.8, 7.6 Hz); 7.14 (4H, m); 7.36 (1H, m); 7.66 (1H, m); 7.92 (1H, dd, 1.4, 4.8 Hz); 8.14 (1H, bs).  
IR (film): 740, 1210, 1240, 1440, 1450, 1470, 1590, 2840, 2940, 3200 and 3450 cm<sup>-1</sup>.

## Example 19

1-(6-Chloro-2-pyridinyl)-4-[3-(1H-indol-3-yl)propyl]piperazine hydrochloride

An acetonitrile solution (25 mL) containing 3-(3-bromopropyl)indole (V; 1.51 g), 1-(6-chloro-2-pyridinyl)-piperazine (III; 2.50 g), micropulverized K<sub>2</sub>CO<sub>3</sub> (1.75 g), and tetrabutylammonium hydrogen sulfate was heated at reflux with stirring and under N<sub>2</sub> atmosphere for 1 h. Excess acetonitrile was removed under pressure and the remaining mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The solid residue was dissolved in water (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried with anhydrous K<sub>2</sub>CO<sub>3</sub>, filtered, and concentrated under reduced pressure to afford a viscous material. Silica gel chromatography (EtOAc:CH<sub>2</sub>Cl<sub>2</sub>; 4:1) yielded the free base (1.67 g; 74%) which was treated with ethanolic HCl to provide the hydrochloride salt of the desired Ia product (1.6 g; 87%).

Anal. Calcd. for C <sub>20</sub> H <sub>23</sub> ClN <sub>4</sub> ·HCl:			
	C, 61.39;	H, 6.19;	N, 14.32
Found:	C, 61.49;	H, 6.24;	N, 14.35.

NMR (DMSO-d<sub>6</sub>): 2.14 (2H, m); 2.80 (2H, t, 6.9 Hz); 3.18 (4H, m); 3.55 (4H, m); 4.36 (2H, d, 13.6 Hz); 6.82 (1H, d, 8.1 Hz); 6.91 (1H, d, 8.1 Hz); 7.05 (3H, m); 7.40 (1H, d, 9.2 Hz); 7.62 (2H, m); 11.00 (1H, bs); 11.55 (1H, bs).

IR (KBr): 740, 785, 950, 1130, 1260, 1440, 1590, 2600, 2920 and 3150 cm<sup>-1</sup>.

## Example 20

1-[3-(1H-indol-3-yl)-propyl]-4-[3-methoxy-2-pyridinyl]piperazine dihydrochloride hydrate

A mixture of 3-(3-bromopropyl)indole (1.55 g), 1-(3-methoxy-2-pyridinyl)piperazine (2.51 g), micropulverized K<sub>2</sub>CO<sub>3</sub> (1.79 g) and tetrabutylammonium hydrogen sulfate (0.11 g) in acetonitrile (100 mL) was heated at reflux under N<sub>2</sub> atmosphere for 3 h. The excess acetonitrile was removed under reduced pressure and water (15 mL) added to the concentrate. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 60 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with sat. NaCl solution, dried with anhydrous K<sub>2</sub>CO<sub>3</sub>, filtered, and concentrated under reduced pressure. Silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 95:5) of the residue yielded the free base which was treated with ethanolic HCl to yield the dihydrochloride salt of the desired Ia product (1.30 g; 45%).

Anal. Calcd. for C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O·2 HCl·0.95 H <sub>2</sub> O:				
	C, 57.27;	H, 6.85;	N, 12.72;	H <sub>2</sub> O, 3.89
Found:	C, 57.67;	H, 6.82;	N, 12.67;	H <sub>2</sub> O, 4.18.

NMR (DMSO-d<sub>6</sub>): 2.16 (2H, m); 2.78 (2H, t, 6.7 Hz); 3.20 (6H, m) 3.57 (2H, d, 12.5 Hz); 3.85 (3H, S);

4.08 (2H, d, 12.5 Hz); 4.80 (3H, bs); 7.02 (4H, m); 7.39 (2H, m); 7.56 (1H, d, 7.8 Hz); 7.81 (1H, dd, 5.8, 0.8 Hz); 10.85 (2H, bs).  
 IR (KBr): 760, 770, 1010, 1255, 1430, 1470, 1555, 1610, 2450, 2910 and 3210  $\text{cm}^{-1}$ .

5

By Process 2. (Ia Products)

### Example 21

10

#### 1-[4-(1H-indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl)piperazine dihydrochloride

15 Borane-methyl sulfide complex (3.3 mL; 2.0 M THF soln.) was added dropwise to a THF (9 mL) solution containing 1-[4-(indol-3-yl)-1-oxobutyl]-4-(3-methoxy-2-pyridinyl)piperazine (IV; 1.0 g) at 0 °C while under N<sub>2</sub> atmosphere. After the addition was complete, the reaction was heated at reflux for 3 h. Upon cooling to 0 °C, MeOH (5 mL) was added and the reaction allowed to stand 20 h at 22 °C. The reaction was cooled to 0 °C and HCl gas introduced until a pH<2 was attained, after which the solution was gently refluxed for 1 h.  
 20 The reaction was cooled, MeOH (10 mL) added, and concentrated under reduced pressure. The residue was heated at reflux in 4 N acetic acid for 5 h. After cooling, the reaction was made basic with 10 N NaOH (pH>10) and extracted with Et<sub>2</sub>O. The combined Et<sub>2</sub>O extracts were dried with anhydrous K<sub>2</sub>CO<sub>3</sub>, filtered, and concentrated under reduced pressure. Silica gel chromatography (EtOAc/MeOH; 97:3) afforded the free base which was treated with ethanolic HCl to provide the dihydrochloride of the desired Ia product (83 mg; 8%).  
 25

30

Anal. Calcd. for C <sub>22</sub> H <sub>28</sub> N <sub>4</sub> O*2 HCl:			
	C, 60.42;	H, 6.92;	N, 12.81
Found:	C, 60.15;	H, 6.78;	N, 12.67.

NMR (DMSO-d<sub>6</sub>): 1.73 (4H, m); 2.74 (2H, t, 6.6 Hz); 3.18 (4H, m); 3.33 (2H, m); 3.53 (2H, d, 12.0 Hz); 4.00 (v, m, bs: CH<sub>2</sub>, H<sup>+</sup>, H<sub>2</sub>O); 3.85 (3H, s); 7.04 (3H, m); 7.16 (1H, d, 2.2 Hz); 7.34 (1H, d, 7.6 Hz); 7.42 (1H, dd, 8.0, 1.2 Hz); 7.52 (1H, d, 7.2 Hz); 7.83 (1H, dd, 5.2, 1.2 Hz).  
 35 IR (KBr): 740, 805, 1000, 1270, 1460, 1550, 1560, 1600, 2570, 2930 and 3250  $\text{cm}^{-1}$ .

### Example 22

40

#### 4-[6-Chloro-2-pyridinyl]-1-[2-(1H-indol-3-yl)-propyl]piperazine

45 To a mixture of 1-(6-chloro-2-pyridyl)piperazine (1.418 g, 7.2 mmol), triethylamine hydrochloride (994 mg, 7.2 mmol) and NaCNBH<sub>3</sub> (1.512 g, 24 mmol) in 12 mL of dry tetrahydrofuran was added a solution of 3-(2-oxopropyl)indole (416 mg, 2.4 mmol) in 5 mL of tetrahydrofuran. The reaction mixture was vigorously stirred at room temperature under Ar for 17 h and then it was poured into saturated aqueous NaHCO<sub>3</sub> and extracted with ethyl acetate (x3). The organic phase was washed with H<sub>2</sub>O (x2) and 0.1N HCl (25 mL) and then it was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a gum. Chromatography (SiO<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>-acetonitrile = 1:1) of this gum gave the product (714 mg, 84%) as a white foam.  
 50 NMR (CDCl<sub>3</sub>)  
 $\delta$ : 7.98 (br s, 1H), 7.64-7.59 (m, 1H), 7.43-7.343 (m, 2H), 7.24-7.08 (m, 2H), 7.06 (d, J=2.3 Hz, 1H), 6.59 (d, J=7.3 Hz, 1H), 6.50 (d, J=8.4 Hz, 1H), 3.62-3.57 (m, 4H), 3.18-3.09 (m, 1H), 3.06-2.93 (m, 1H), 2.79-2.74 (m, 4H), 2.65 (dd, J=13.5, 9.1 Hz, 1.03 (d, J=6.5 Hz, 3H)).  
 55 The hydrochloride was prepared by treating an ethereal solution of the product with anhydrous HCl. The resulting white fluffy solid was crystallized from ethanol-ether to give the hydrochloride salt (660 mg, 85%) as a white, microcrystalline solid: m.p. 242-244 °C (dec).

By Process 3 (Ib and Ic Products)

## Example 23

3-[4-[4-(6-Chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxy-1H-indole

A solution of 5-methoxyindole (0.26 g, 1.8 mmole), 4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-cyclohexan-1-one (VIII; 0.50 g, 1.7 mmole), and pyrrolidine (0.5 mL) in ethanol (10 mL) was refluxed for 18 h. The solution was concentrated in vacuo and the residue chromatographed on silica gel using ethyl acetate as the eluent to give the desired product of formula Ib (0.59 g, 82%, m.p. 210-213 °C).

Anal. Calcd. for C <sub>27</sub> H <sub>27</sub> ClN <sub>4</sub> O:			
	C, 68.16;	H, 6.44;	N, 13.25
Found:	C, 68.00;	H, 6.57;	N, 12.97

NMR(DMSO-d<sub>6</sub>): 1.52 (1H, m); 2.04 (1H, m), 2.22 (1H, m); 2.40 (2H, m); 2.64 (6H, m); 3.48 (4H, m); 3.75 (3H, s); 8.07 (1H, m); 6.63 (1H, d, 7.4 Hz); 6.75 (2H, m); 7.26 (3H, m); 7.53 (1H, dd, 7.9, 8.1 Hz); 10.91 (1H, bs).  
IR (KBr): 780,800, 980, 1140, 1260, 1450, 1480, 1550, 1600, 2840 and 2920 cm<sup>-1</sup>.

## Example 24

3-[4-[4-(Substituted-2-pyridinyl)-1-piperazinyl]-1-cyclohexan-1-yl]-1H-indole

4-(1H-indol-3-yl)cyclohex-3-enone, ethylene ketal, XII

Indole (1.17 g, 10 mmol), 1,4-cyclohexanedione mono-ethylene ketal (1.95 g, 12.5 mmol), and pyrrolidine (1.77 g, 25 mmol, 2.1 mL) were refluxed in ethanol (50 mL) for 3 days. The solution was concentrated in vacuo. The residue was washed with ethyl acetate (30 mL) and the solid product was collected and dried (yield: 2.05 g, 80%). The product was recrystallized from methanol (20 mL) to give compound XII as a white powder (1.75 g).

4-(1H-indol-3-yl)cyclohexanone, XI

Compound XII (1.75 g, 6.9 mmol) was hydrogenated for 18 h at 60 psi using 10% Pd/C (0.15 g). The mixture was filtered and the filtrate concentrated in vacuo. The residue was refluxed for 18 h in acetone (150 mL) with water (10 mL) and p-toluene sulfonic acid (0.10 g). Sodium carbonate (5.0 g) was added and the mixture refluxed for 30 min. The mixture was cooled and filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate as the eluent to give the XI desired product (1.29 g, 88%).

3-[4-(4-(Substituted-2-pyridinyl)-1-piperazinyl)-1-cyclohexyl]-1H-indole, Ic

A mixture of compound II (10 mmol), the desired substituted-pyridinyl piperazine (III; 10 mmol), and titanium(IV) isopropoxide (3.72 mL, 12.5 mmol) would be remaining ketone band (gentle heating may be required). The viscous solution would then be diluted with ethanol (10-20 mL) and sodium

cyanoborohydride (0.42 g, 6.7 mmol) added. After stirring for 20 hr, water (2 mL) would be added and the resulting inorganic precipitate filtered and washed with ethanol. The filtrate could then be concentrated in vacuo and the crude product purified by chromatography on silica gel. Alternately, cyclohexenyl products of Formula Ib may be hydrogenated to yield products of Formula Ic in cases where other substituents on the precursor molecule are stable to the hydrogenation process.

Compound preparation data for these and other Formula I compounds, prepared in a manner similar to the above procedures, is shown in Table 1. Selection of appropriate starting materials and intermediates as well as adjustments of the procedures would be well within the skill of one skilled in the art.

**Table 1**  
**Formula I Compounds**

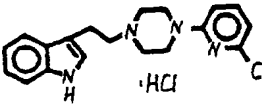
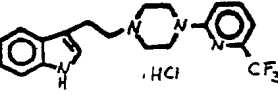
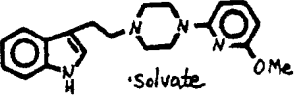
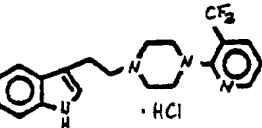
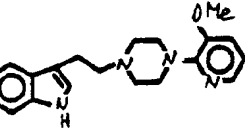
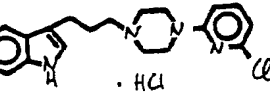
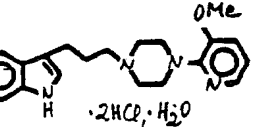
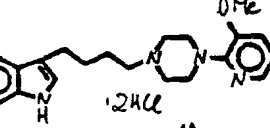
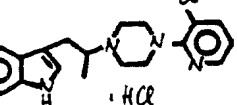
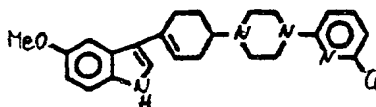
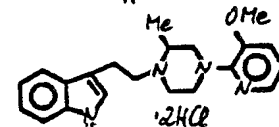
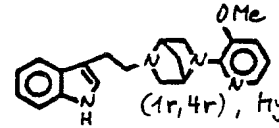
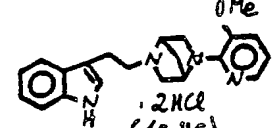
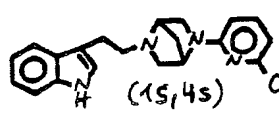
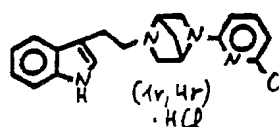
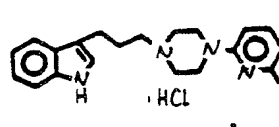
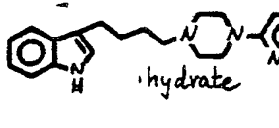
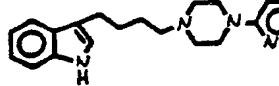
<u>Ex. No.</u>	<u>Structure</u>	<u>Yield</u>	<u>MP (°C)</u>	<u>Cryst. Sol.</u>
14		77	250-252	EtOH
15		68	206-208	EtOH
16		89	60-85	EtOH
17		80	242-243	EtOH
18		44	138-140	EtOH
19		87	221-222	EtOH
20		45	216-219	EtOH
21		23	228-230	EtOH
22				

Table 1 (continued)

## Formula I Compounds

5

Ex. No.	Structure	Yield	MP(°C)	Cryst. Sol.
23		82	210-213	EtOAc
25	 ·2HCl	11	155-194	EtOH
26	 (1r, 4r), hydrate	4	55-60	EtOH
27	 ·2HCl (1s, 4s)	43	234-236	iPrOH/EtOH/ THF
28	 (1s, 4s)	67	239-241	iPrOH/EtOH
29	 (1r, 4r) ·HCl	53	239-242	iPrOH/EtOH
30	 ·HCl	14	212-214	Hex/CH <sub>2</sub> Cl <sub>2</sub>
31	 hydrate	-1	99-101	EtOH
32		50	83-86	Hex/CH <sub>2</sub> Cl <sub>2</sub>

50

55

### Formula I Compounds

50

Table 1 (continued)

## Formula I Compounds

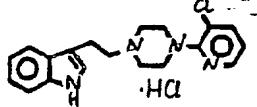
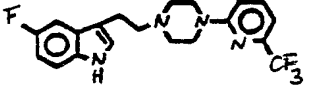

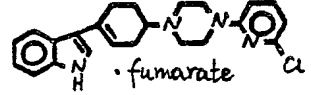
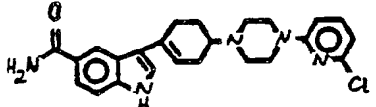
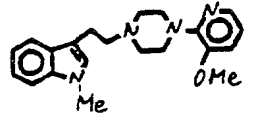
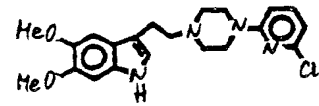
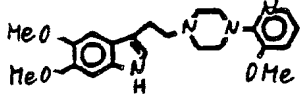
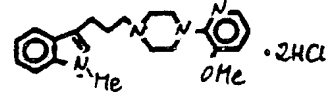
Ex. No.	Structure	%Yield	MP(°C)	Cryst. Sol.
42		42	213-216	EtOH
43		43	115-116	Ethyl acetate/ hexane
44		31	140-142	Ethyl acetate/ hexane
45		66	226-230	MeOH
46		63	225-230	10% MeOH/ EtOAc
47		46	125-127	Ethyl acetate
48		45	137-139	Ethyl acetate
49		42	160-163	Ethyl acetate
50		92	187-189	EtOH



Table 1 (continued)

## Formula I Compounds

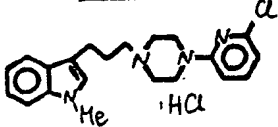
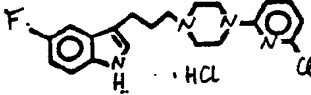
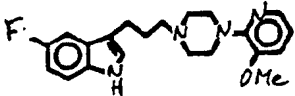
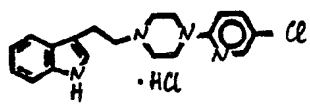
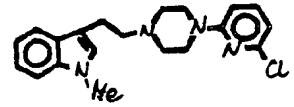
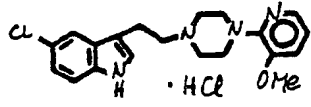
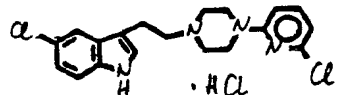
Ex. No.	Structure	Yield	MP(°C)	Cryst. Sol.
51		83	200-203	EtOH
52		81	210-212	EtOH
53		72	127	CH <sub>2</sub> Cl <sub>2</sub> /Et <sub>2</sub> O/ hexane
54		38	253-255	EtOH
55		72	115-116	Ethyl acetate
56		41	205-207	Ethyl acetate
57		40	238-242	MeOH/Et <sub>2</sub> O

Table 2

Biological Activities of Formula I Compounds:			
Inhibition of Serotonin Uptake ( in vitro )			
Ex. No.	IC <sub>50</sub> (nM)	Ex. No.	IC <sub>50</sub> (nM)
14	74	36	75
15	73	37	386
16	88	38	11
17	37	39	0.2
18	13	40	177
19	98	41	2.8
20	1.1	42	520
21	58	43	73
23	99	44	560
25	8.6	45	100
26	106	46	27
27	12.5	47	24
28	77	48	127
29	106	50	3.7
30	192	51	86
31	27	54	30
32	259	55	126
33	105		
34	5.6		
35	152		

#### Additional Detailed Description of the Invention

Some additional compounds of Formula I have been made, tested and found to have useful CNS properties, particularly antidepressant properties. The additional compounds were prepared by employing the synthetic processes described hereinabove, using alterations which would be apparent to a skilled chemist in order to produce the desired product compound. Some additional examples are give here for further guidance.

#### Additional Intermediate Compounds.

#### Compounds of Formula III

#### Example 58

#### 1-(6-Chloro-2-pyridinyl)-2-methylpiperazine

A mixture of 2-methylpiperazine (21.31 g), 2,6-dichloropyridine (10.0 g) and micropulverised K<sub>2</sub>CO<sub>3</sub> (27.99 g) in CH<sub>3</sub>CN (200 mL) was heated at reflux under nitrogen atmosphere for 24 h. The reaction was filtered and the filtrate concentrated under reduced pressure. The concentrate was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and

extracted with 5% NaHCO<sub>3</sub> and water. The organic phase was dried with K<sub>2</sub>CO<sub>3</sub>, filtered and concentrated under reduced pressure. Silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH; 96:4:0.4) of the residue yielded product, (13.34 g, 93%).

5

## Example 59

10 1-(3-methoxy-2-pyridinyl)-2-methylpiperazine

A mixture of 2-methylpiperazine (6.66 g) and 2-bromo-3-methoxypyridine (2.5 g) was heated in an autoclave at 100 °C for 24 h. The reaction mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and extracted with 5% NaHCO<sub>3</sub> and water. The organic phase was dried with K<sub>2</sub>CO<sub>3</sub>, filtered, and concentrated under reduced pressure.  
15 Silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH; 92:8:0.8) of the residue yielded the product (2.28 g, 83 %).

## Example 60

20

1-(5-Chloro-3-methoxy-2-pyridinyl)piperazine

25

## a) 2-bromo-5-chloro-3-pyridinol

A solution of bromine (12.35 g) in 10% NaOH (70 ml) was added dropwise with stirring to a solution of 5-chloro-3-pyridinol (10.00 g) in 10% NaOH (70 ml). After the addition was complete, the reaction was stirred at 22 °C for 20 h. The reaction was cooled to 0 °C and acidified to pH 5.3 with concentrated HCl (aq). The precipitate was filtered and dried under vacuum for 60 h to afford a) (15.66 g, 97 %).  
30

## b) 2-bromo-5-chloro-3-methoxypyridine

35

To a stirred mixture of 2-bromo-5-chloro-3-pyridinol (15.66 g) and pulverized KOH (16.79 g) in DMSO (100 ml) at 55 - 60 °C was added dropwise a solution of CH<sub>3</sub>I (13.27 g) in DMSO (35 ml) while under nitrogen atmosphere. After the addition was complete, the reaction was maintained at 55 - 60 °C for 1 h. The reaction was extracted with Et<sub>2</sub>O (3 x 150 ml) and the combined Et<sub>2</sub>O extracts were treated in turn with 40 1N NaOH (150 ml), water (150 ml), 1N HCl (150 ml), water (150 ml) and a saturated NaCl solution (150 ml). The organic phase was dried with MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to yield a solid material. Recrystallization of the solid from hexane afforded b) (3.52 g, 21 %).

45 c) 1-(5-chloro-3-methoxy-2-pyridinyl)piperazine

Anhydrous piperazine (13.41 g) and 2-bromo-5-chloro-3-methoxypyridine (3.50 g) were heated in an autoclave at 100 °C for 20 h. The mixture was dissolved in water (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 100 mL). The combined organic extracts were washed with a saturated NaCl solution, dried with K<sub>2</sub>CO<sub>3</sub>,  
50 filtered, and concentrated under reduced pressure. Silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 90:10) of the residue yielded product (1.17 g, 33%).

## Compounds of Formula V

55

## Example 61

3-(2-Bromoethyl)-1-methylindole

## a) Methyl 1-methylindole-3-acetate

5

A dispersion of 35% KH in oil (21.0 g, 0.18 mol) was washed free of oil with dry pentane under an Ar atmosphere. To a suspension of the resulting solid in 100 ml of dry dimethylformamide was added a solution of indole-3-acetic acid (10.5 g, 0.060 mol) in 60 ml of dimethylformamide, dropwise at -20 °C under Ar. The mixture was stirred at the same temperature for 2 h and then CH<sub>3</sub>I (12.0 ml, 0.19 mol) was added dropwise. Stirring was continued at -20 ° to 10 °C for 2 1/2 h and then the mixture was stored at 5 °C for 16 h. Ether was then added and the mixture was washed (H<sub>2</sub>O, brine), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give an orange oil. Flash chromatography (SiO<sub>2</sub>/10-20% ethyl acetate-hexane x 2) of this oil afforded the product (5.25 g, 43%) as an oil: IR (neat) 1745 cm<sup>-1</sup>; <sup>1</sup>Hnmr (80 MHz, CDCl<sub>3</sub>) δ 7.75-7.55 (m, 1H), 7.40-7.07 (m, 4H), 3.83 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H).

15

## b) 3-(2-Hydroxyethyl)-1-methylindole

To a suspension of LiAlH<sub>4</sub> (2.0 g, 0.052 mol) in 50 mL of dry tetrahydrofuran was added dropwise a solution of methyl 1-methylindole-3-acetate (5.25 g, 0.026 mol) in 70 mL of dry tetrahydrofuran at -10 °C under Ar. The mixture was refluxed for 1 h and then it was cooled at 0 °C and quenched by the sequential addition of 2 mL of H<sub>2</sub>O, 2 mL of 15% aqueous NaOH and finally 6 mL of H<sub>2</sub>O. The resulting slurry was filtered and the filter cake was washed with additional tetrahydrofuran. Evaporation of the filtrate gave the product (4.0 g, 89%) as an oil which was used without further purification.

25

## c) 3-(2-Bromoethyl)-1-methylindole

To a solution of 1-methyl-3-(2-hydroxyethyl)indole (4.00 g, 0.023 mol) in 50 mL of acetonitrile at -20 °C under Ar was added a solution of CBr<sub>4</sub> (10.16 g, 0.031 mol) in 25 mL of acetonitrile, followed by a solution of triphenylphosphine (8.00 g, 0.031 mol) in 125 mL of acetonitrile. The mixture was stirred and allowed to warm to 0 °C over 2 h. The resulting mixture was evaporated and the residue was chromatographed (SiO<sub>2</sub>/hexane, then ethyl acetate-hexane = 1:4) to give the product (4.00 g, 74%) as a brown oil: IR (neat) 2940, 1617, 1552 cm<sup>-1</sup>; <sup>1</sup>Hnmr (200 MHz, CDCl<sub>3</sub>) δ 7.58 (d, J = 7.6 Hz, 1H), 7.33-7.09 (m, 3H), 6.95 (s, 1H), 3.77 (s, 3H), 3.62 (t, J = 7.9 Hz, 2H), 3.32 (t, J = 7.7 Hz, 2H).

35

## Example 62

40

3-[1-Methyl-3-(p-toluenesulfonyloxy)propyl]indole

To a suspension of LiAlH<sub>4</sub> (1.50 g, 39 mmol) in 100 mL of dry THF at -10 °C under Ar was added a solution of ethyl 3-(3-indolyl)-3-methylpropionate<sup>1</sup> (7.00 g, 30 mmol) in 50 mL of THF. The mixture was stirred at room temperature for 3 h and then it was quenched at 0 °C with 2 mL of H<sub>2</sub>O. The resulting slurry was filtered and the filter cake was washed with THF. The filtrate was then dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give the intermediate VI product, 3-(1-methyl-3-hydroxypropyl)indole (5.05 g, 88%) as an oil: IR (neat) 3420, 3300 cm<sup>-1</sup>.

50

To an ice cold solution of 3-(1-methyl-3-hydroxypropyl)indole (5.00 g, 0.026 mol) in 100 mL of CH<sub>2</sub>Cl<sub>2</sub> was added triethylamine (4.1 mL, 0.03 mol), p-toluenesulfonyl chloride (5.50 g, 0.029 mol) and 4-N,N-dimethylaminopyridine (DMAP) (0.6 g). The mixture was stirred at room temperature under Ar for 18 h and then it was evaporated and the residue was chromatographed (SiO<sub>2</sub>/ethyl acetate-hexane = 1:9, then ethyl acetate) to give the product (7.75 g, 86%) as a light brown gum: IR (neat) 3420, 1357, 1175 cm<sup>-1</sup>.

55

1. Oikawa, et al., Tetrahedron Lett., 1759 (1978).

## Additional Formula I Compounds.

## Example 36 - Alternate Preparation

3-[2-[4-(6-Chloro-2-pyridyl)-1-piperazinyl]propyl]-indole

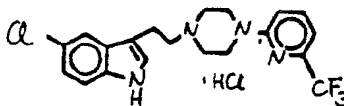
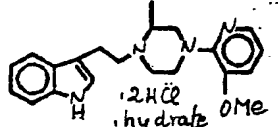

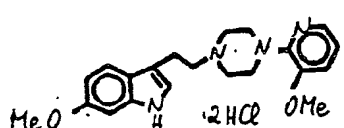
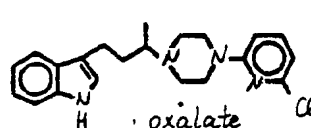
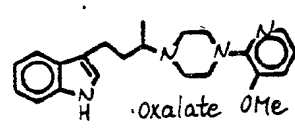
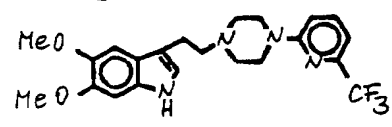
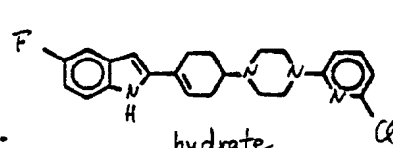
10 To a mixture of 1-(6-chloro-2-pyridyl)piperazine (1.418 g, 7.2 mmol), triethylamine hydrochloride (994 mg, 7.2 mmol) and NaCNCH<sub>3</sub> (1.512 g, 24 mmol) in 12 mL of dry tetrahydrofuran was added a solution of 3-(2-oxopropyl)indole (416 mg, 2.4 mmol) in 5 mL of tetrahydrofuran. The reaction mixture was vigorously stirred at room temperature under Ar for 17 h and then it was poured into saturated aqueous NaHCO<sub>3</sub> and extracted with ethyl acetate (x3). The organic phase was washed with H<sub>2</sub>O (x2) and 0.1 N HCL (25 mL) and  
 15 then it was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a gum. Chromatography (SiO<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>-acetonitrile = 1:1) of this gum gave the product (714 mg, 84%) as a white foam: <sup>1</sup>Hnmr (200 MHz, CDCl<sub>3</sub>) δ 7.98 (br s, 1H), 7.64-7.59 (m, 1H), 7.43-7.343 (m, 2H), 7.24-7.08 (m, 2H), 7.06 (d, J = 2.3 Hz, 1H), 6.59 (d, J = 7.3 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 3.62-3.57 (m, 4H), 3.18-3.09 (m, 1H), 3.06-2.93 (m, 1H), 2.79-2.74 (m, 4H), 2.65 (dd, J = 13.5, 9.1 Hz, 1H), 1.03 (d, J = 6.5 Hz, 3H). The hydrochloride salt was prepared by treating an ethereal  
 20 solution of the product with anhydrous HCl. The resulting white fluffy solid was crystallized from ethanol-ether to give the hydrochloride salt (660 mg, 85%) as a white, micro-crystalline solid: m.p. 242-244 °C (dec); IR (KBr) 3430, 3190, 1590 cm<sup>-1</sup>.

Additional Formula I compounds which have been prepared by appropriate modifications of the reaction schemes and procedures given hereinabove, are displayed in Table 1A.

Table 1A  
Additional Formula I Compounds

5

10

Ex. No.	Structure	% Yield	MP (°C)	Cryst. Sol.
63	 ·HCl	49	158-62	Me <sub>2</sub> CO-Et <sub>2</sub> O
64	 ·2HCl hydrate	53	174-85	EtOH-ET <sub>2</sub> O
65		69	103-05	EtOAc
66	 ·2HCl	41	218	MeOH-Et <sub>2</sub> O
67	 oxalate	44	110-115	MeOH-THF
68	 oxalate	30	55	Et <sub>2</sub> O
69		43	122-25	EtOAc
70	 hydrate	15	168-170	EtOAc

55

Table 1A (cont.)  
Additional Formula I Compounds

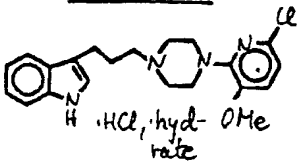
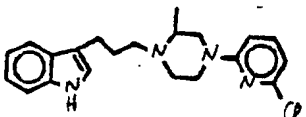
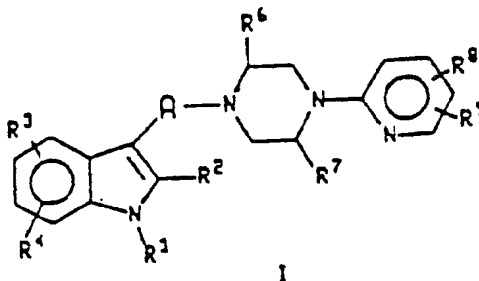
Ex. No.	Structure	% Yield	MP (°C)	Cryst. Sol.
71		65	194-98	EtOH
72		65	132-35	EtOH

Table 2A

Biological Activities of Some Additional Formula I Compounds			
Inhibition of Serotonin Uptake ( in vitro )			
Ex. No.	IC <sub>50</sub> (nM)	Ex. No.	IC <sub>50</sub> (nM)
56	<1	67	142
57	166	68	36.7
63	437	69	479
64	<1	70	141
65	134	71	4.9
66	35.9	72	18.7

## Claims

1. A compound of Formula I and the pharmaceutically acceptable acid addition salts thereof,



wherein

R<sup>1</sup> and R<sup>2</sup> are independently selected from lower, meaning C<sub>1-4</sub>, alkyl or hydrogen;

R<sup>3</sup>, R<sup>4</sup>, R<sup>8</sup> and R<sup>9</sup> are independently selected from hydrogen, lower alkyl, lower alkoxy, carbamide, halogen, trifluoromethyl and thio-lower alkyl, with the proviso that R<sup>8</sup> and R<sup>9</sup> cannot both be hydrogen at the

same time;

A is a C<sub>5-7</sub> cycloalkanyl or cycloalkenyl ring, or

A is



10 wherein n is an integer from 1 to 3 and R<sup>5</sup> is the same as R<sup>1</sup>; and  
R<sup>6</sup> and R<sup>7</sup> are independently selected from hydrogen, methyl or R<sup>6</sup> and R<sup>7</sup> can be taken together as a methylene bridge.

2. The compound of claim 1 wherein A is a C<sub>5-7</sub> cycloalkanyl or cycloalkenyl ring.

3. The compound of claim 1 wherein A is



20 4. The compound of claim 1 wherein R<sup>6</sup> and R<sup>7</sup> are selected from hydrogen or methyl.

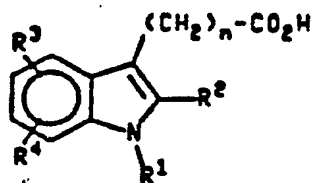
5. The compound of claim 1 wherein R<sup>6</sup> and R<sup>7</sup> are taken together as a methylene bridge.

6. The compounds of claim 1: 1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
1-[2-(1H-indol-3-yl)ethyl]-4-(3-trifluoromethyl-2-pyridinyl)piperazine ;  
1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methylpiperazine ;  
25 1-[2-(1H-indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1]heptane ;  
1-[2-(1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;  
1-[2-(1H-indol-3-yl)ethyl]-4-(6-methoxy-2-pyridinyl)piperazine ;  
1-[2-(1H-indol-3-yl)ethyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1]heptane ;  
1-[3-(1H-indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
30 1-[3-(1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)piperazine ;  
1-[4-(1H-indol-3-yl)butyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
1-[2-(1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;  
2-[2-(1H-indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane ;  
35 2-[2-(1H-indol-3-yl)ethyl]-5-(6-chloro-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane ;  
1-[3-(1H-indol-3-yl)propyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;  
1-[4-(1H-indol-3-yl)butyl]-4-(6-chloro-2-pyridinyl)piperazine ;  
1-[4-(1H-indol-3-yl)butyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;  
1-[3-(1H-indol-3-yl)propyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazine ;  
40 2-[3-(1H-indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1S,4S)-2,5-diazabicyclo[2.2.1] heptane ;  
2-[3-(1H-indol-3-yl)propyl]-5-(3-methoxy-2-pyridinyl)-(1R,4R)-2,5-diazabicyclo[2.2.1] heptane ;  
1-[2-(1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)-2-methylpiperazine ;  
1-[2-(1H-indol-3-yl)ethyl]-4-(4-trifluoromethyl-2-pyridinyl)piperazine ;  
1-[2-(5-methoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
45 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
1-[2-(5-methoxy-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;  
1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;  
1-[2-(1H-indol-3-yl)ethyl]-4-(3-chloro-2-pyridinyl)piperazine ;  
1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;  
50 1-[2-(5-methoxy-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;  
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-methoxyindole ;  
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole ;  
3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-1H-indole-5-carboxamide ;  
1-[2-(N-methyl-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
55 1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
1-[3-(N-methyl-1H-indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
1-[3-(N-methyl-1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)piperazine ;



- 1-[3-(5-fluoro-1H-indol-3-yl)propyl]-4-(6-chloro-2-pyridinyl)piperazine ;  
 1-[3-(5-fluoro-1H-indol-3-yl)propyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
 1-[2-(1H-indol-3-yl)ethyl]-4-(5-chloro-2-pyridinyl)piperazine ;  
 1-[2-[N-methyl-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;  
 5 1-[2-(5-chloro-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)piperazine ;  
 1-[2-(5-chloro-1H-indol-3-yl)ethyl]-4-(6-chloro-2-pyridinyl)piperazine ;  
 1-[2-(5-chloro-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;  
 1-[2-(1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-2-methyl-piperazine ;  
 4-(6-chloro-2-pyridinyl)-1-[2-(6-methoxy-1H-indol-3-yl)ethyl]-piperazine ;  
 10 1-[2-(6-methoxy-1H-indol-3-yl)ethyl]-4-(3-methoxy-2-pyridinyl)-piperazine ;  
 1-[3-(1H-indol-3-yl)-3-methylpropyl]-4-(6-chloro-2-pyridinyl)-piperazine ;  
 1-[3-(1H-indol-3-yl)-3-methylpropyl]-4-(3-methoxy-2-pyridinyl)-piperazine ;  
 1-[2-(5,6-dimethoxy-1H-indol-3-yl)ethyl]-4-(6-trifluoromethyl-2-pyridinyl)piperazine ;  
 3-[4-[4-(6-chloro-2-pyridinyl)-1-piperazinyl]-1-cyclohexen-1-yl]-5-fluoro-1H-indole ;  
 15 4-(5-chloro-3-methoxy-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-piperazine hydrochloride ;  
 4-(6-chloro-2-pyridinyl)-1-[3-(1H-indol-3-yl)propyl]-2-methyl-piperazine ;  
 7. A process for preparing the compounds of claims 1 to 6 characterized in that A) a compound of the general formula II:

20



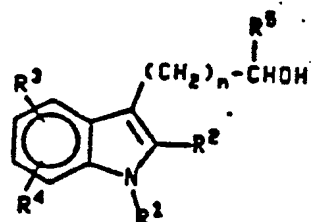
25

(II)

30

is reacted with a compound of the general formula  $R^5-M$ , wherein M represents a metalloid species, to obtain a compound of the general formula VI:

35



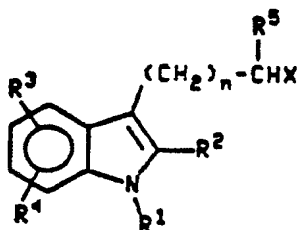
40

(VI)

45

a compound of the general formula VI is reacted with a reagent Y-X, wherein X is a leaving group and Y is a hydrogen atom or a counter ion, to obtain a compound of the general formula V:

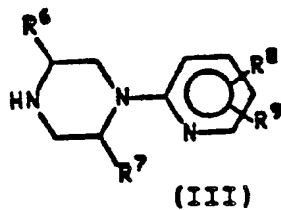
50



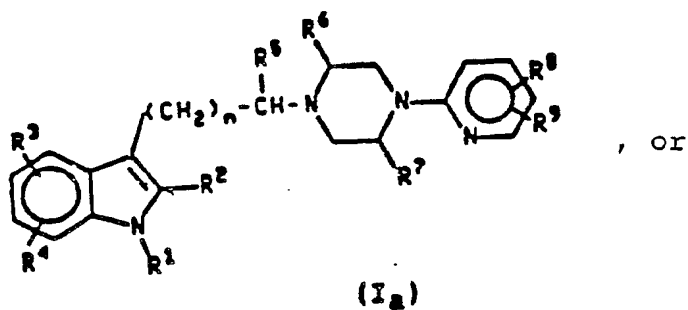
55

(V)

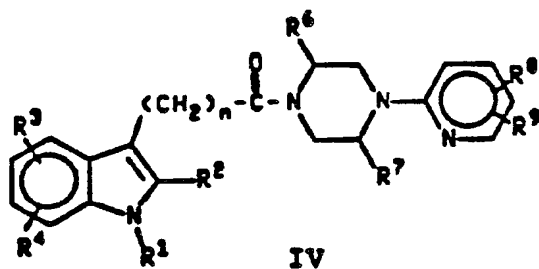
a compound of the general formula V is reacted with a compound of the general formula III:



to obtain a compound of the general formula Ia

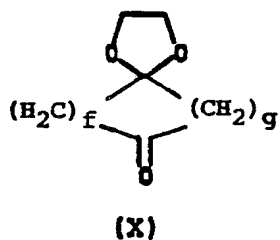


B) a compound of the general formula II or an active equivalent thereof is reacted with a compound of the general formula III to obtain a compound of the general formula IV:



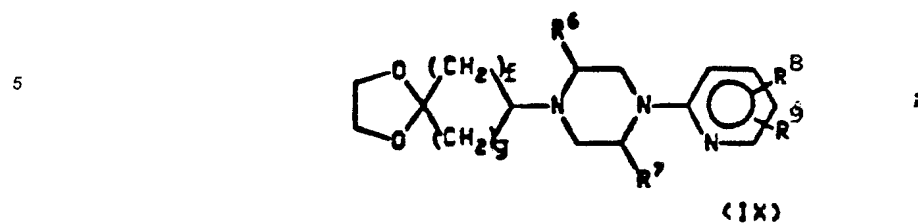
a compound of the general formula IV is reacted with  $R^5-M$ , wherein  $R^5$  is defined as above, to obtain a compound of the general formula Ia, or

C) a compound of the general formula III is reductively alkylated with a compound of the general formula X

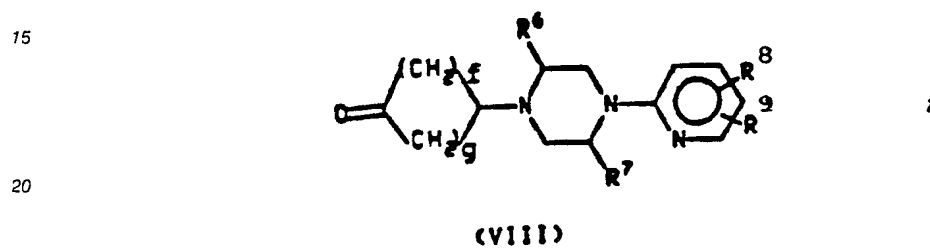


wherein f and g are integers from 0 to 5 with the proviso that  $f + g$  must be equal to 3, 4 or 5, to give a

compound of the general formula IX:



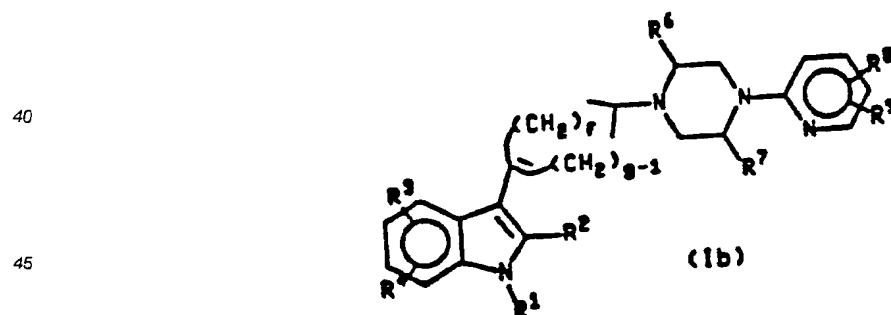
a compound of the general formula IX is deprotected to produce a compound of the general formula VIII



25 a compound of the general formula VIII is condensed with a compound of the general formula VII

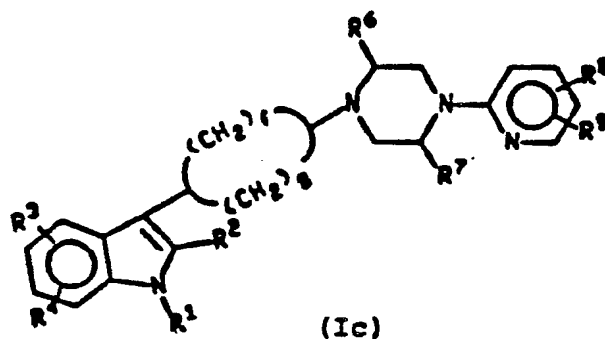


35 to give a compound of the general formula Ib



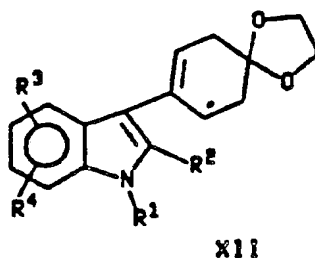
50 and, if desired, a compound of the general formula Ib is reduced to a compound of the general formula Ic:

55

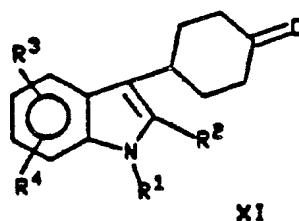


15 or

D) a compound of the general formula VIII is condensed with a compound of the general formula X to give a compound of the general formula XII



30 a compound of the general formula XII is reduced and deketalized to a compound of the general formula XI:



40 a compound of the general formula XI is condensed with a compound of the general formula III to give a compound of the general formula Ic, the symbols R<sup>1</sup> through R<sup>9</sup> and n being defined as in claim 1, and if desired, a so obtained compound of formula I is converted to a pharmaceutically acceptable acid addition salt thereof.

45

8. A pharmaceutical composition comprising at least one compound of claim 1 to 6, optionally together with a pharmaceutical carrier and/or adjuvant.

9. A pharmaceutical composition of claim 8 in dosage unit form suitable for systemic administration to a mammalian host comprising a pharmaceutical carrier and from about 1 to 500 mg of at least one compound of claims 1 to 6.

50

10. A process for preparing the pharmaceutical compositions of claims 8 or 9 which comprises providing at least one compound of claims 1 to 6 in a form suitable for systemic administration, preferably in dosage unit form, and optionally incorporated into a pharmaceutical carrier.

11. The use of at least one compound of claims 1 to 6 for preparing a pharmaceutical composition for ameliorating an undesirable state of depression in a mammal.

55



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X,D	US-A-3 562 278 (S. ARCHER) * Claim 1, page 1 * -----	1,11	C 07 D 401/12 C 07 D 401/14 A 61 K 31/44 A 61 K 31/495 C 07 D 487/08
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 401/00 C 07 D 487/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 01-09-1989	Examiner CASADO Y MARTIN DE MERCA
<div>CATEGORY OF CITED DOCUMENTS</div> <div><div>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</div><div>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... &amp; : member of the same patent family, corresponding document</div></div>			